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PRINCIPAL INVESTIGATOR: Mindy S. Kurzer, Ph.D.

CONTRACTING ORGANIZATION: University of Minnesota
Minneapolis, MN 55455-2070

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Mindy S. Kurzer, Ph.D.

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
University of Minnesota
Minneapolis, MN 55455-2070

E-Mail: mkurzer@umn.edu

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13. ABSTRACT (Maximum 200 Words)

The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing phytoestrogens; 2) phytoestrogen-free soy powder; or 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of prostate cancer risk factors, including serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3α, 17β-androstanediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biops will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA and androgen receptor density. At this point, seven subjects have begun the feeding study and biological samples have been collected, processed and stored.

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INTRODUCTION

The low risk of prostate cancer in Asia is thought to be due to dietary factors, including soy consumption. Studies showing an inverse association between prostate cancer risk and urinary excretion of soy phytoestrogens suggest that phytoestrogens contribute to the cancer-preventive effects of soy. One mechanism by which soy phytoestrogens are thought to be cancer-preventive is *via* reduction of endogenous sex hormones known to stimulate prostate cell growth. Despite the interest in soy phytoestrogens for prevention of prostate cancer, there have been no studies in men to evaluate the effects of soy phytoestrogen consumption on sex steroids and prostate tissue biomarkers, and no studies evaluating effects of phytoestrogen metabolism on sex steroids in men.

The main objective of this project is to evaluate the effects of soy phytoestrogen consumption on reproductive hormones and prostate tissue markers of cell proliferation and androgen action in men at high risk of prostate cancer. The underlying hypothesis is that alteration of endogenous hormones is a mechanism by which soy phytoestrogens prevent prostate cancer.

The specific aims of this study are to compare the effects of consumption of phytoestrogen-containing soy protein, phytoestrogen-free soy protein, and milk protein, on risk factors for prostate cancer (endogenous hormones, prostate specific antigen, prostate tissue markers of cell proliferation and hormone action), in men at high risk for prostate cancer. Comparing the three groups will enable us to distinguish the specific effects of soy phytoestrogens from effects caused by other soy components. A randomized parallel arm study will be performed, in which 90 men at high risk of prostate cancer will be randomized to receive one of three dietary supplements for six months: 1) soy powder containing 1 mg phytoestrogens/kg body weight; 2) phytoestrogen-free soy powder; and 3) phytoestrogen-free milk powder. Urine and blood will be collected at 0, 3 and 6 months, for evaluation of serum hormones (testosterone, dihydrotestosterone, androstenedione, dehydroepiandrosterone, estradiol, estrone, 3α, 17β-androstanediol glucuronide, sex hormone binding globulin) and prostate specific antigen, as well as urinary estrogen and phytoestrogen metabolites. Before and after the intervention, prostate biopsies will be performed to evaluate prostate tissue expression of apoptosis (TUNEL assay, Bax, Bcl-2), proliferation (Ki67, PCNA), and androgen receptor density.

Data from *in vitro*, animal and epidemiological studies suggest that androgens and estrogens play a role in prostate carcinogenesis. Soy phytoestrogens have been shown to alter sex steroids in women in a potentially beneficial direction, yet such studies in men have not been reported. Studies of the hormonal effects of soy phytoestrogens in men will contribute to our knowledge of the cancer-preventive mechanisms of soy phytoestrogens, and may lead to dietary recommendations for prevention of prostate cancer.

BODY

According to the original statement of work, the following tasks were to be performed during the first year of this project:

Task 1: Hire and train staff, coordinate with Veteran's Administration and Fairview-University Hospital staff, establish all study protocols (months 0-2)

Task 2: Perform feeding study on cohort #1 (30 men)

- Recruit 30 men at high risk of prostate cancer (cohort #1) and randomize into three intervention groups: phytoestrogen-containing soy protein, phytoestrogen-free soy protein, or milk protein
- Perform feeding study; process and store serum, urine and biopsy slides
- Analyze samples from cohort #1: serum hormones and SHBG by RIA; serum free and total PSA by ELISA; urine estrogen metabolites and phytoestrogens by GC-MS; biopsy slides by immunohistochemistry

Although the grant officially began on April 15, 2002, final approval from the DOD IRB was not received until January 2003. As a result, we were not able to begin the project until February 2003. Between April 2002 and January 2003, the following tasks were accomplished:

- Obtained approval from three institutional review boards: the Minneapolis VA Medical Center, where we are recruiting subjects and collecting biological samples; the University of Minnesota; and the Department of Defense.
- Finalized the study design
  - Chose all protein powders for intervention (offer sugared and sugar-free)
  - Finalized biological endpoints
  - Finalized subject inclusion/exclusion criteria
  - Ordered research materials
- Designed all research forms
  - Subject handbook
  - Subject recording calendars
  - Physician orders
  - Lab and clinic protocols
- Developed collaboration between Veteran's Hospital and University of Minnesota's research lab
  - Arranged regular meetings
  - Disseminated correspondence among investigators and technicians
- Conducted orientation sessions
  - Presented study hypothesis, design, dietary protocol, and collection procedures
  - Coordinated clinical visits for study participants
  - Maintained rapport with subjects
- Developed protocols for sample collection, processing and storage

Since February 2003, ten men have qualified for the study. Nine of these men were oriented and signed consent forms, and seven have begun the feeding study. Two of the men who were oriented withdrew from the study due to difficulties with the protocol (limiting alcohol intake and maintaining body weight). We hope to increase the rate of recruitment by using sugar-free protein powders to accommodate type II diabetics and investigating additional recruitment sites. We anticipate that recruitment will increase as retirees return to Minnesota from having spent the winter in warmer climates.

KEY RESEARCH ACCOMPLISHMENTS

- Received IRB approval from three institutions: The VA Medical Center, the University of Minnesota, and the Dept. of Defense
- Developed successful collaboration with researchers at the VA Medical Center
- Trained staff
- Planned and developed protocols for all aspects of the study
- Successfully recruited first seven subjects and began feeding study
- Developed methods for collecting, processing, and storing biological samples, and performed them successfully with the first group of subjects

REPORTABLE OUTCOMES

None at this time

CONCLUSIONS

The human feeding study has successfully begun and biological samples have been processed and are being stored as stated in the study design. At this point there are no reportable data from which to draw conclusions.

REFERENCES

None

APPENDICES

None